Causes of Infertility as Predictors of Subsequent Cancer Risk

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Background: Although studies have found elevated risks of certain cancers linked to infertility, the underlying reasons remain unclear.
Methods: In a retrospective cohort study of 12,193 U.S. women evaluated for infertility between 1965 and 1988, 581 cases of cancer were identified through 1999. We used standardized incidence ratios (SIRs) to compare cancer risk with the general population. Analyses within the cohort estimated rate ratios (RRs) associated with infertility after adjusting for other risk predictors.
Results: Infertility patients demonstrated a higher cancer risk than the general population (SIR = 1.23; 95% confidence interval [CI] = 1.1–1.3), with nulligravid (primary infertility) patients at even higher risk (1.43; 1.3–1.6). Particularly elevated risks among primary infertility patients were observed for cancers of the uterus (1.93) and ovaries (2.73). Analyses within the cohort revealed increased RRs of colon, ovarian, and thyroid cancers, and of melanomas associated with endometriosis. Melanomas were linked with anovulatory problems, whereas uterine cancers predominated among patients with tubal disorders. When primary infertility patients with specific causes of infertility were compared with unaffected patients who had secondary infertility, endometriosis was linked with distinctive excesses of cancers of the colon (RR = 2.40; 95% CI = 0.7–8.4), ovaries (2.88; 1.2–7.1), and thyroid (4.65; 0.8–25.6) cancers, as well as melanomas (2.32; 0.8–6.7). Primary infertility due to anovulation particularly predisposed to uterine cancer (2.42; 1.0–5.8), and tubal disorders to ovarian cancer (1.61; 0.7–3.8). Primary infertility associated with male-factor problems was associated with unexpected increases in colon (2.85; 0.9–9.5) and uterine (3.15; 1.0–9.5) cancers.
Conclusions: The effects of infertility may extend beyond gynecologic cancers. Thyroid cancers and melanomas deserve specific attention, particularly with respect to endometriosis.

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Numerous studies have demonstrated that infertile women are at an increased risk of certain cancers, including cancers of the breast, ovary, and uterus.[1] Although studies have suggested that this risk may be attributable to underlying reasons for the infertility, results have been inconclusive, possibly reflecting imprecise information on the causes of infertility. Case–control studies have had to rely on patient reports of these causes, with many women being unable to provide accurate information. Cohort studies generally have reported more accurate information but have often been hampered by small numbers and limited information on other predictors of cancer risk.

Among the causes of infertility that have received attention in previous studies are anovulation, endometriosis, and tubal factors. Some,[2–4] but not all,[5–7] studies have reported anovulatory problems to be associated with increases in breast cancer, as well as with uterine cancer risk,[8–10] particularly if associated with polycystic ovarian disease.[11] Endometriosis has been found to be associated with ovarian cancers in clinical[12,13] as well as epidemiologic studies[14–17] and, in several investigations,[15,17] also with breast cancer. Furthermore, several studies have found that patients with tubal disorders have elevated risks of ovarian cancer.[16,18,19] Less well investigated are relationships with cancers other than breast or gynecologic cancers, although studies have suggested potential links of anovulatory disorders with melanoma[20] and of endometriosis with non-Hodgkin lymphoma.[15,17,21]

We conducted a large retrospective cohort study of women treated for infertility at 5 specialized practices to evaluate cancer risk as related to various causes of infertility. We have previously addressed relationships of causes of infertility to ovarian cancer,[22] confirming an excess risk

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associated with endometriosis. The present analysis evaluates other cancers, including several that have received less attention. We considered sites with possible hormonal etiologies, including colon and thyroid cancers, as well as melanomas.

METHODS

The methods of this investigation have been previously described.[22,23] In brief, eligible study subjects comprised women who had sought advice for infertility at 5 large reproductive endocrinology practices in Boston, MA; Chicago, IL; Detroit, MI; Palo Alto, CA; and New York City, NY. These practices were chosen because they had retained all original records and had evaluated large numbers of infertile patients. The study was approved by the institutional review boards at the collaborating centers as well as at the National Cancer Institute.

Patients were eligible for inclusion in the study if they had a U.S. address at the time of evaluation and if they were seen more than once or had been referred with relevant medical information by another physician. Patients with primary infertility (those who had never been able to conceive) or secondary infertility were eligible for study inclusion, but those who were evaluated for reversal of a tubal ligation were not. A total of 12,193 patients met eligibility criteria. Data entered directly into laptop computers by trained abstractors included patient identifiers, information on the infertility work-ups (all procedures and tests), detailed drug information, menstrual and reproductive histories, and other factors that might affect health status (eg, weight).

Information on current residence of the patients was sought through telephone directories, credit bureaus, postmasters, and motor vehicle administration records. Additional information was obtained by administering questionnaires to located, living subjects and through linkage of the cohort with selected cancer registries and the National Death Index (NDI). As shown in Figure 1, a total of 9751 (80%) of the patients were successfully traced 1 or more years after first clinic registration. Of these, 1319 (11%) indicated upon contact that they did not want to participate in the study and would not allow access to data in their medical records. For these patients, only descriptive information (ie, calendar year at registration, age at registration, and race) was retained.

A total of 272 patients were traced as deceased. Questionnaires were mailed to remaining traced patients beginning in early 1998, with telephone follow-up attempted for nonrespondents. A total of 5597 of the patients completed a questionnaire. The questionnaire ascertained information on demographic factors, updated health status, and lifestyle factors that could affect health, including the following: menstrual, pregnancy and breastfeeding history; use of exogenous hormones; anthropometric factors; cigarette and alcohol consumption; and breast and ovarian disease screening history. An additional 216 patients had follow-up visits at least 1 year beyond their initial clinic visit, with clinic records available for data extraction. For 2347 patients for whom we were unable to obtain questionnaire data, we had accurate location information that enabled tracing through cancer registries in the states in which the majority of the patients were last known to reside—namely California, Florida, Illinois, Massachusetts, Michigan, New Jersey, New York, and Texas.

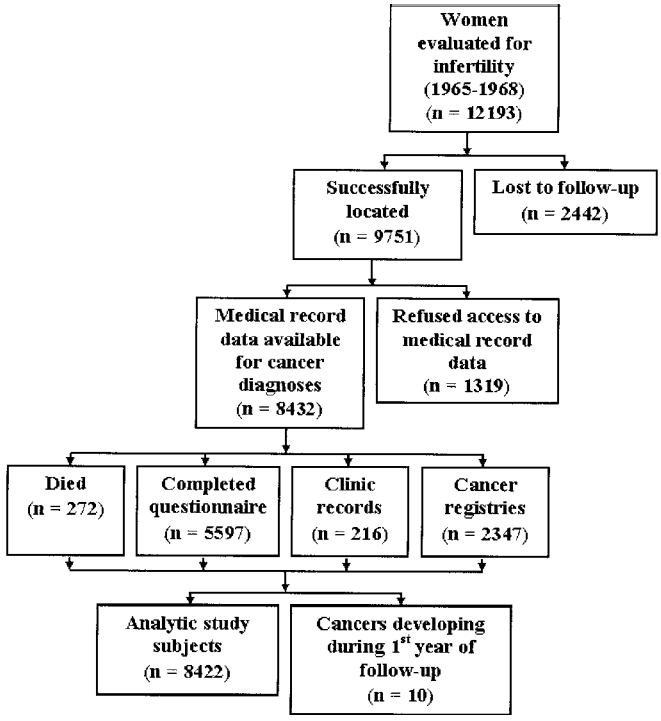

FIGURE 1. Status of tracing and questionnaire administration among eligible study subjects.

Attempts were made to medically verify cancers reported in the questionnaires through obtaining discharge summaries, operative reports, and pathology reports from the institutions where the diseases had been diagnosed or treated. Additional information was obtained from cancer registries or the NDI or from copies of obtained death certificates. Self-reported cancers that were found to be benign after medical record review (1 colon, 2 breast, 12 cervical, 2 uterine, 6 ovarian, 1 vaginal, 1 vulvar cancers; 11 melanomas; 1 leukemia) were eliminated, leaving 581 cancers for analysis. The proportion with medical documentation varied by cancer site, from a low of 26% for melanoma to a high of 96% for respiratory tract cancers (Table 1).

Statistical Methods

Person-years were accrued beginning 1 year after the date of first evaluation for infertility and continuing through the earliest date of cancer occurrence, death, or date last known alive and free of cancer (as indicated by questionnaire, linkage against cancer registry data, or last clinic visit).

TABLE 1. Standardized Incidence Ratios Comparing Cancer Risk Among Infertile Patients With the General Population*

Cancer	Observed No.†	No. With Medical Confirmation	Expected No.	SIR‡ (95% CI)
All sites§	581	453	475.5	1.23 (1.1–1.3)
Buccal cavity, pharynx	5	5	6.5	0.77 (0.2–1.8)
Colon	28	24	15.9	1.76 (1.2–2.6)
Rectum	6	6	9.0	0.67 (0.2–1.5)
Pancreas	5	5	3.9	1.27 (0.4–3.0)
Trachea, bronchus, lung	28	27	28.9	0.97 (0.6–1.4)
Breast	292	247	226.5	1.29 (1.2–1.5)
Invasive	243	198	188.1	1.29 (1.1–1.5)
In situ	49	49	38.4	1.28 (0.9–1.7)
Cervix	14	6	23.0	0.61 (0.3–1.0)
Uterine corpus	39	27	24.9	1.57 (1.1–2.1)
Ovary	45	31	22.7	1.98 (1.4–2.7)
Kidney	7	5	6.1	1.14 (0.5–2.4)
Melanoma	42	11	26.7	1.57 (1.1–2.1)
Brain	7	7	6.7	1.04 (0.4–2.1)
Thyroid	18	13	18.1	0.99 (0.6–1.6)
Lymphatic tumors	24	18	26.0	0.92 (0.6–1.4)
Non-Hodgkin lymphoma	11	8	12.7	0.86 (0.4–1.5)
Hodgkin disease	1	1	3.8	0.26 (0.0–1.5)
Multiple myeloma	2	1	2.3	0.88 (0.1–3.2)
Leukemia	10	8	7.2	1.39 (0.7–2.6)

*Based on data from the Surveillance, Epidemiology and End Results (SEER) Program.
†Only cancers with 5 or more observed cases are shown. Additional cancers among cohort members included the following sites: 4 stomach, 1 liver, 2 bladder, 1 eye, 1 other endocrine, 1 bone, and 3 connective tissue.
‡Number of observed cancers divided by the expected number based on age, race, and calendar year-specific SEER incidence rates.
§Excluding nonmelanotic skin cancers.

Patients with cancer registry searches had variable study ending dates, ranging from the end of 1997 to 1999, depending on the completeness of registration in their states. Otherwise, 31 December 1999 defined the end of the study period. Patients lost to follow-up after their initial clinic visit, those who denied access to their records, and 10 patients who were diagnosed with cancer during the first year of follow-up were excluded from further analyses (Fig. 1), leaving 8,422 analytic study subjects and 155,527 woman-years of follow-up.

We calculated standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) by dividing the number of observed cancers among the infertility patients by the expected number based on age, race and calendar year-specific disease incidence rates for women available through the Surveillance Epidemiology and End Results (SEER) Program.

Additional analyses were conducted within the cohort of infertile women, allowing multivariable adjustment for numerous risk factors. Rate ratios (RRs) and their 95% CIs for developing cancer associated with types and causes of infertility were estimated by Poisson regression using standard likelihood ratio methods.[24] For all analyses, the RRs were adjusted for age at risk (<40, 40–49, 50+ years) and calendar year of follow-up (before 1980, 1980–1989, 1990 or later). Other factors, such as study site and race, were included in the regression models, as necessary, to evaluate their roles as potential confounding factors or to examine variations of the RRs. In addition, we used data obtained through questionnaires to assess confounding and modifying influences of other cancer predictors, including reproductive status at follow-up, age at first birth, family history of cancer, body mass, and exposure to exogenous hormones.

RESULTS

The median year at first evaluation was 1978, when subjects were on average 30 years of age. Nearly 80% of the subjects were known to be white. There were no substantial

differences according to calendar year or age at first evaluation between the subjects included in the analyses and those excluded for various reasons (see Fig. 1); however, a larger proportion of the subjects excluded from analyses had missing information on race. The median length of follow-up was 18.8 years, with over 80% of the study population followed for 15 or more years. Forty-three percent of the women presented with primary infertility (ie, no prior pregnancies).

Comparisons With the General Population

A total of 581 of the infertile patients were identified as developing a subsequent cancer, compared with 475.5 cancers expected based on general population rates (1.23; 1.1–1.3; Table 1). Individual sites that were substantially elevated were cancers of the colon (1.76; 1.2–2.6), breast (1.29; 1.2–1.5), uterine corpus (1.57; 1.1–2.1) and ovaries (1.98; 1.4–2.7), and melanoma (1.57; 1.1–2.1). Most other observed cancers were close to expectation, although the risk of cervical cancer was somewhat reduced (0.61; 0.3–1.0).

The risk of cancer was somewhat higher among patients evaluated for primary infertility (1.43; 1.3–1.6) than among those with secondary infertility (1.27; 1.1–1.4; Table 2). This elevation primarily reflected higher risks attributable to primary infertility for uterine (1.93) and ovarian (2.73) cancers.

Comparisons Within the Population of Infertile Women

Given the inability of comparisons with the general population to account for patient characteristics other than age and race, the majority of analyses focused on comparisons within the cohort of infertile women. As detailed elsewhere,[22] patients were classified, according to a standardized algorithm, into 6 potentially overlapping causes, based on whether they had received a workup adequate to rule in or out each infertility condition, and, if so, whether there was evidence to support that particular cause of infertility. Of those adequately evaluated for each condition, 36% showed evidence of endometriosis, 28% anovulation, 43% tubal disease /pelvic adhesions, 32% male factor, 11% cervical disorders, and 19% uterine disorders. The completeness of workups varied, with some patients evaluated for only 1 cause (6%) and other patients evaluated for all 6 causes (34%). Of the patients who were adequately evaluated for all causes of infertility, only 308 (11%) were found not to have any cause (ie, unexplained infertility). A number of patients had multiple causes of infertility (eg, 13% of the patients had both endometriosis and anovulation).

Internal analyses which assessed relationships according to a specific cause of infertility took into account the completeness of the evaluation, as well as results for other causes. Other risk factors were evaluated as potential confounders but had minimal impact on the derived risk estimates. These other variables included eventual gravidity (which varied little by the causes of infertility) as well as detailed measures of exposure to ovulation-stimulating drugs (including dose and latency effects), which, as detailed elsewhere,[23,25] were not convincingly related to ovarian or breast cancer risk in this study.

TABLE 2. Standardized Incidence Ratios of Cancers Among Infertility Patients by Type of Infertility (Primary vs. Secondary)

	Primary Infertility Patients		Secondary Infertility Patients	
Cancer Site*	**Observed No.**	**SIR (95% CI)**	**Observed No.**	**SIR (95% CI)**
All sites†	260	1.43 (1.3–1.6)	321	1.27 (1.1–1.4)
Colon	12	1.84 (0.9–3.2)	16	1.71 (0.9–2.8)
Trachea, bronchus, lung	13	1.10 (0.6–1.9)	15	0.81 (0.4–1.3)
Breast	124	1.30 (1.1–1.6)	168	1.28 (1.1–1.5)
Cervix	8	0.82 (0.4–1.6)	6	0.45 (0.2–0.9)
Uterine corpus	20	1.93 (1.2–3.0)	19	1.30 (0.8–2.0)
Ovary	26	2.73 (1.8–4.0)	19	1.44 (0.9–2.3)
Melanoma	17	1.49 (0.9–2.4)	25	1.63 (1.1–2.4)
Brain	5	1.75 (0.6–4.1)	2	0.51 (0.1–1.9)
Thyroid	9	1.16 (0.5–2.2)	9	0.87 (0.4–1.6)
Lymphatic tumors	9	0.82 (0.4–1.6)	15	0.99 (0.6–1.6)
Non-Hodgkin lymphoma	3	0.56 (0.1–1.6)	8	1.08 (0.5–2.1)
Leukemia	5	1.65 (0.5–3.9)	5	1.20 (0.4–2.8)

*Only sites with 5 or more observed cancers among women with either primary or secondary infertility are shown.
†Excluding nonmelanotic skin cancers.

Primary infertility persisted as a contributor of risk for uterine (1.54; 0.8–2.9) and ovarian (1.99; 1.1–3.6) cancers (Table 3). These analyses incorporated censoring of patients at the time of removal of their uterus or both ovaries. A seemingly more important risk factor for both sites was whether patients remained nulligravid throughout follow-up, with the associated RRs for uterine and ovarian cancers rising to 2.24 and 2.36, respectively. These risks, however, were less stable than those associated with gravidity at entry, given that information on gravidity at follow-up was dependent on acquiring completed patient questionnaires. Neither gravidity at entry or at follow-up was an important predictor for most other cancers, with the exception of thyroid cancer, which was based on small numbers. After simultaneous adjustment for other causes of infertility as well as gravidity at entry, patients with endometriosis were at an elevated risk of cancers of the colon (2.00; 0.7–5.4), ovaries (1.25; 0.6–2.6), and thyroid (3.09; 0.9–10.7), as well as melanomas (2.06; 1.0–4.4). In contrast to reports elsewhere,[15,17,21] we observed no enhanced risk of non-Hodgkin lymphoma among patients with endometriosis (data not shown), although our ability to assess the association was limited by small numbers of events. Anovulation was linked with somewhat elevated risks of melanoma (1.53; 0.8–2.9), and tubal diseases or pelvic adhesions with uterine cancers (1.39; 0.7–2.9). Male factor was associated with increases in the risk of colon (1.95; 0.7–5.6) and uterine (2.13; 0.9–4.6) cancers.

Given our observations of differential risks of certain cancers by type of infertility (primary vs. secondary), we conducted further internal analyses cross-classifying types and causes of infertility (Table 4). We compared all women with those hypothesized to be at the lowest risk of a certain cause of infertility, namely patients without evidence of that cause who presented with secondary infertility. This analysis showed that women with primary infertility due to endometriosis had elevated risks of cancers of the colon (2.40; 0.7–8.4), ovaries (2.88; 1.2–7.1), and thyroid (4.65; 0.8–25.6), as well as melanomas (2.32; 0.8–6.7). Primary infertility due to anovulation seemed to particularly predispose to uterine cancers (2.42; 1.0–5.8) and tubal disorders to ovarian cancers (1.61; 0.7–3.8). Patients whose primary infertility was due to male-factor problems were at particularly increased risks of colon (2.85; 0.9–9.5) and uterine (3.15; 1.0–9.5) cancers.

DISCUSSION

In this study, we found that women with infertility are at a 23% higher risk of cancer than women in the general population, a result comparable with findings from other cohort investigations.[7,10,26,27] Also consistent with other studies were our findings that infertile women, particularly those with primary infertility, are at an increased risk of uterine and ovarian cancers.

We took an approach different from that of previous studies that have classified causes of infertility; we allowed women to be classified with multiple causes, and we considered specific causes only among women who had received workups adequate to rule in or rule out conditions. Thus, our prevalence for most conditions was considerably higher than in other investigations, and only patients who were evaluated

TABLE 3. Rate Ratios* of Selected Cancer Sites Among Infertile Women by Types and Causes of Infertility

Types and Causes of Infertility	Colon (n = 28) RR (95% CI)	Breast (n = 292) RR (95% CI)	Uterine† (n = 39) RR (95% CI)	Ovary‡ (n = 45) RR (95% CI)	Melanoma (n = 42) RR (95% CI)	Thyroid (n = 18) RR (95% CI)
Primary vs. secondary infertility at initial evaluation	1.01 (0.5–2.2)	1.02 (0.8–1.3)	1.54 (0.8–2.9)	1.99 (1.1–3.6)	0.91 (0.5–1.7)	1.33 (0.5–3.4)
Nulligravid vs. gravid at follow-up	1.08 (0.4–3.2)	1.05 (0.8–1.5)	2.24 (1.0–5.1)	2.36 (1.2–4.8)	1.14 (0.5–2.5)	2.42 (0.8–7.2)
Causes of infertility						
Endometriosis	2.00 (0.7–5.4)	0.78 (0.6–1.1)	0.82 (0.3–1.9)	1.25 (0.6–2.6)	2.06 (1.0–4.4)	3.09 (0.9–10.7)
Anovulation	0.46 (0.2–1.3)	1.12 (0.9–1.4)	1.13 (0.6–2.3)	1.01 (0.5–2.0)	1.53 (0.8–2.9)	0.73 (0.2–2.3)
Tubal disease/ pelvic adhesions	1.12 (0.5–2.8)	1.04 (0.8–1.4)	1.39 (0.7–2.9)	0.88 (0.4–1.7)	0.93 (0.5–1.9)	0.64 (0.2–2.0)
Male factor	1.95 (0.7–5.6)	1.21 (0.9–1.6)	2.13 (0.9–4.6)	0.96 (0.4–2.0)	0.83 (0.4–1.8)	0.67 (0.2–2.5)

*All models adjusted for age at follow-up, calendar time, study sites, gravidity at entry, and all causes of infertility. Additional adjustment for other risk factors (eg, age at first birth, family history of cancer, hysterectomy/ovarian status at follow-up, obesity, or use of estrogen replacement therapy, oral contraceptives, or ovulation-stimulating drugs) did not appreciably change risk estimates.

†Uterine corpus. Women censored at time of hysterectomy, leaving 8392 analysis subjects with 145,755 women-years accrued.

‡Women censored if both ovaries removed, leaving 8362 analysis subjects and 148,221 women-years accrued.

TABLE 4. Rate Ratios* of Selected Cancer Sites Among Infertile Women by Combinations of Types and Causes of Infertility

Combinations of Types and Causes of Infertility	Colon (n = 28) RR (95% CI)	Breast (n = 292) RR (95% CI)	Uterine (n = 39) RR (95% CI)	Ovary (n = 45) RR (95% CI)	Melanoma (n = 42) RR (95% CI)	Thyroid (n = 18) RR (95% CI)
Endometriosis						
No, primary infertility	0.94 (0.2–4.0)	0.93 (0.7–1.3)	1.25 (0.5–3.2)	1.72 (0.7–4.3)	1.23 (0.4–3.7)	1.44 (0.2–10.2)
Yes, secondary infertility	1.25 (0.3–5.3)	0.72 (0.5–1.1)	0.84 (0.3–2.7)	0.69 (0.2–2.4)	2.18 (0.8–6.1)	2.89 (0.5–17.5)
Yes, primary infertility	2.40 (0.7–8.4)	0.82 (0.5–1.3)	1.00 (0.3–3.2)	2.88 (1.2–7.1)	2.32 (0.8–6.7)	4.65 (0.8–25.6)
Anovulation						
No, primary infertility	1.14 (0.5–2.6)	0.99 (0.7–1.3)	1.16 (0.5–2.5)	2.80 (1.4–5.8)	1.02 (0.5–2.2)	1.28 (0.4–3.7)
Yes, secondary infertility	0.61 (0.2–2.2)	1.06 (0.8–1.5)	0.92 (0.3–2.6)	1.88 (0.7–4.7)	1.75 (0.8–3.9)	0.68 (0.3–3.3)
Yes, primary infertility	0.33 (0.1–2.6)	1.19 (0.8–1.7)	2.42 (1.0–5.8)	1.50 (0.5–4.7)	1.27 (0.5–3.5)	1.01 (0.2–4.9)
Tubal disease/pelvic adhesions						
No, primary infertility	1.16 (0.4–3.5)	1.09 (0.8–1.5)	1.95 (0.7–5.2)	1.36 (0.6–2.9)	0.98 (0.4–2.3)	2.62 (0.7–10.5)
Yes, secondary infertility	1.22 (0.4–3.9)	1.12 (0.8–1.6)	1.55 (0.5–4.4)	0.59 (0.2–1.6)	0.94 (0.4–2.3)	1.11 (0.2–5.8)
Yes, primary infertility	1.20 (0.3–4.4)	1.02 (0.7–1.5)	2.20 (0.7–6.5)	1.61 (0.7–3.8)	0.90 (0.3–2.5)	1.06 (0.2–6.7)
Male factor						
No, primary infertility	0.54 (0.1–2.8)	0.74 (0.5–1.1)	1.72 (0.6–5.1)	1.44 (0.6–3.3)	1.60 (0.7–3.6)	1.05 (0.3–3.9)
Yes, secondary infertility	0.48 (0.1–4.1)	0.90 (0.6–1.3)	2.51 (0.8–7.8)	0.69 (0.2–2.5)	1.83 (0.7–4.6)	0.49 (0.1–4.2)
Yes, primary infertility	2.85 (0.9–9.5)	1.28 (0.9–1.8)	3.15 (1.0–9.5)	1.72 (0.7–4.8)	0.23 (0.0–1.8)	0.90 (0.2–4.7)

*Reference group is women with secondary infertility who do not have the indicated causes of infertility. All models adjusted for age at follow-up, calendar time, study sites, gravidity at entry, and all causes of infertility.

for all of our 6 causes of infertility would have been eligible to be labeled as having unexplained infertility. Our analyses also differed from most other investigations in that we were able to make comparisons not only with the general population but also within the population of infertile patients, allowing us to clarify the distinctive effects of causes of infertility independent of other cancer predictors.

Endometriosis and anovulatory problems are the 2 major classifications of infertility that have been of most interest in previous investigations of cancer risk. We confirmed several previous observations, and noted several new findings that may warrant further investigation.

Women with endometriosis had elevated risks of ovarian cancer (findings detailed elsewhere[22]). Ovarian cancer was particularly enhanced for women diagnosed with primary infertility. Contrary to the observations of others,[15,17] we observed no excess risk of breast cancer related to a diagnosis of endometriosis. We also did not detect a relationship with non-Hodgkin lymphoma, as has been found elsewhere,[15,17,21] although our power to assess this relationship was limited given that we observed only 11 such malignancies.

A somewhat unexpected finding in our study was an excess risk of melanoma among patients with endometriosis, with such patients having an RR that exceeded 2. A limitation was that a large proportion of melanomas in our study were not medically confirmed, leading to questions regarding the specificity of the relationship. However, this is not the first investigation to report an association between endometriosis and melanoma. High risks of melanoma were noted both in a survey of 4000 women conducted by the Endometriosis Association[17] and in a follow-up study of 3,940 college alumnae[28]; in the latter investigation, the relationship was restricted to subjects with red hair. Our finding may reflect that endometriosis is more common among women with red hair,[29] a phenotype recognized as predisposing to melanoma.[30] However, an earlier study of nonredheads observed a connection between endometriosis and dysplastic nevi,[31] a recognized precursor of melanoma. In contrast, a large case-control study failed to document an association with endometriosis, although this finding was presumably based on few women with such histories.[32] It is therefore unclear whether endometriosis is a true risk factor for melanoma or merely a reflection of correlated risk factors.

Another cause of infertility receiving specific attention in our study was anovulation. Similar to previous studies that have focused on women with hormonal causes of infertility, we found high risks of uterine cancers among women with anovulatory disorders,[9,10] most likely reflecting an influence of estrogens unopposed by progestogens. Of interest in our study was a particularly enhanced risk of uterine cancers associated with primary infertility, possibly reflecting unique hormonal perturbations among these women. We attempted

to assess the potential contribution of polycystic ovarian syndrome, associated with uterine cancer elsewhere,[3,8–10] but only a small proportion of women (401 or 5%) in our study were classified with this syndrome according to recently published criteria.[33]

Previous investigations[2–4] have noted high risks of breast cancer among infertile women diagnosed with ovulatory problems, although defined in various ways (eg, progesterone deficiency, chronic anovulation syndrome, hormonal subfertility). Our comparisons with either the general population or with other infertile patients showed at most only a modest increase in breast cancer risk associated with anovulation. Thus, our results are more comparable with other cohort studies that also were able to account for reproductive behavior.[6,34] In fact, the Nurses' Health Study,[6] which included 251 breast cancer cases, found a substantial reduction in the risk of breast cancer among anovulatory women (0.4; 0.2–0.9).

Because previous studies have suggested that patients with tubal ligations are at a decreased risk of ovarian cancer,[35] blocked tubes could in theory similarly reduce risk. We found little evidence for a reduced risk of ovarian cancer among patients with tubal disorders, and in fact we observed primary infertility patients with tubal disorders to be at somewhat higher risk than other infertile patients. Our findings are consistent with several investigations that have found higher ovarian cancer risks among patients with fallopian tube dysfunction[19] or pelvic inflammatory disease.[16,18] This lends further support to the notion of inflammation as an important agent in ovarian carcinogenesis.[36] In contrast, risks of other cancers were not distinctively affected by histories of pelvic diseases or adhesions.

Our study also had some ability to examine risks related to several other cancers that have been suggested as having possible hormonal etiologies, including cancers of the colon, thyroid and cervix. Given suggestions of a possible inverse relation between parity and colon cancer,[37] we were interested in assessing whether infertile patients might be at high risk. Although our patients demonstrated an elevated risk compared with the general population, there was no major difference in risk between those evaluated for primary as opposed to secondary infertility. This suggests that the elevated risk might merely be a reflection of more intensive surveillance for this cancer. The unexpected finding of an elevated RR for this cancer among patients with endometriosis (a diagnosis that depended on surgical evaluation) might also be a reflection of close medical scrutiny. Also of interest was thyroid cancer, which was not elevated overall, but was elevated among patients with endometriosis. The risk was particularly apparent when patients with primary infertility were compared with those who had secondary infertility not associated with endometriosis. Although we were limited in our ability to further assess this association, given that only 7 women with endometriosis developed thyroid cancer, our finding is in line with a previous investigation that observed a nonsignificant excess of thyroid cancer among endometriosis patients[15] and with findings that endometriosis patients often exhibit thyroid and other autoimmune disorders.[38,39] Finally, of interest was our observation of a low rate of cervical cancer among infertile women, in line with a well-established adverse effect of parity on this cancer.[40]

A number of our patients were diagnosed with male-factor problems, and these patients (particularly those with primary infertility) had high risks of developing colon or uterine cancers. A biologic explanation for this association is not readily obvious. Because patients evaluated for male-factor problems had lower rates of evaluation for other causes of infertility, the elevated risks that were associated with male factor may reflect the possibility that these patients had other undiagnosed causes of infertility. Alternatively, patients worked up exclusively for male-factor problems may have had other attributes associated with a high risk of developing certain cancers, including higher social class, which has been linked to elevations for both colon and uterine cancers. In addition, higher eventual rates of nulligravidity may have played a role, since, of all the causes of infertility, patients with male-factor infertility demonstrated the highest rates of primary infertility at initial clinic evaluation.

In summary, this study confirmed that infertile patients are at an elevated risk of developing certain cancers, including cancers of the uterine corpus and ovary, and, to a lesser extent, breast cancer. Patients evaluated for primary infertility were generally at higher risks than those with secondary infertility. The highest risks were seen for selected cancers due to certain causes of primary infertility. These included links of endometriosis with ovarian and possibly thyroid cancer and melanoma, of anovulatory problems with uterine cancer, and of tubal disorders with ovarian cancer.

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